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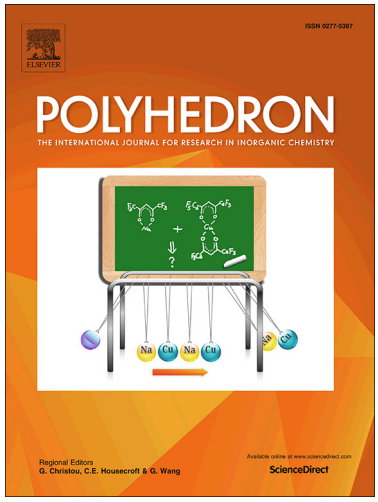

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Synthesis and crystal structures of chiral ferrocene and ruthenocene substituted aminomethylnaphthols obtained through Betti-condensation

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Abstract

Ferrocene- and ruthenocenecarboxaldehydes have been employed in Betti-type condensation reactions with 2-naphthol and (*S*)-phenylethylamine to give metallocenyl-substituted aminomethylnaphthols in a diastereomerically pure form. The absolute configurations of the new chiral compounds have been determined by means of NMR experiments and confirmed by X-ray crystallography. The chiral metallocenyl-aminomethylnaphthols have been tested as pre-catalysts for the addition of diethyl zinc to aldehydes, with enantioselectivities of up to 88% ee.

Keywords: Chiral metallocenes; absolute configuration; crystal structures; chiral ligands; diethyl zinc.

1. Introduction

The aminobenzylation of 2-naphthol using the three component "Betti condensation reaction" [1] has gained significant interest over the last decade due to the opportunity to control the stereoselectivity. The scope of the current knowledge on the synthesis and application of aminobenzylnaphthols has recently been demonstrated in review articles [2]. In a new development of this reaction, the use of chiral enantiopure amines resulted in the highly diastereoselective formation of aminobenzylnaphthols, which were applied for enantioselective transformations [3]. The three component condensation can be performed with a practicable "one pot" reaction protocol, by simple mixing of 2-naphthol, the chiral amine and aldehyde, often without application of solvent. In most cases, the "Betti reaction" is performed with variations of the amine [4] and aldehyde [3c,e,n,4b-e,g,h,5] components, using 2-naphthol as the third component. Reports that describe the application of substituted 2-naphthols or 1-naphthol within the "Betti condensation" are rare [3c,4c,j,6]. Only recently has the diastereoselective condensation of a chiral amine, aldehydes and dihydroxy naphthalene been described [7]. There are also reports describing similar reactions, although these employ non-chiral variants [4i,8]. The aldehyde component of the "Betti condensation" is usually an aromatic aldehyde. The application of aliphatic aldehydes has been presented only in isolated examples and seems to be a low-yielding exceptional case [3c,e,i,k,4j,9].

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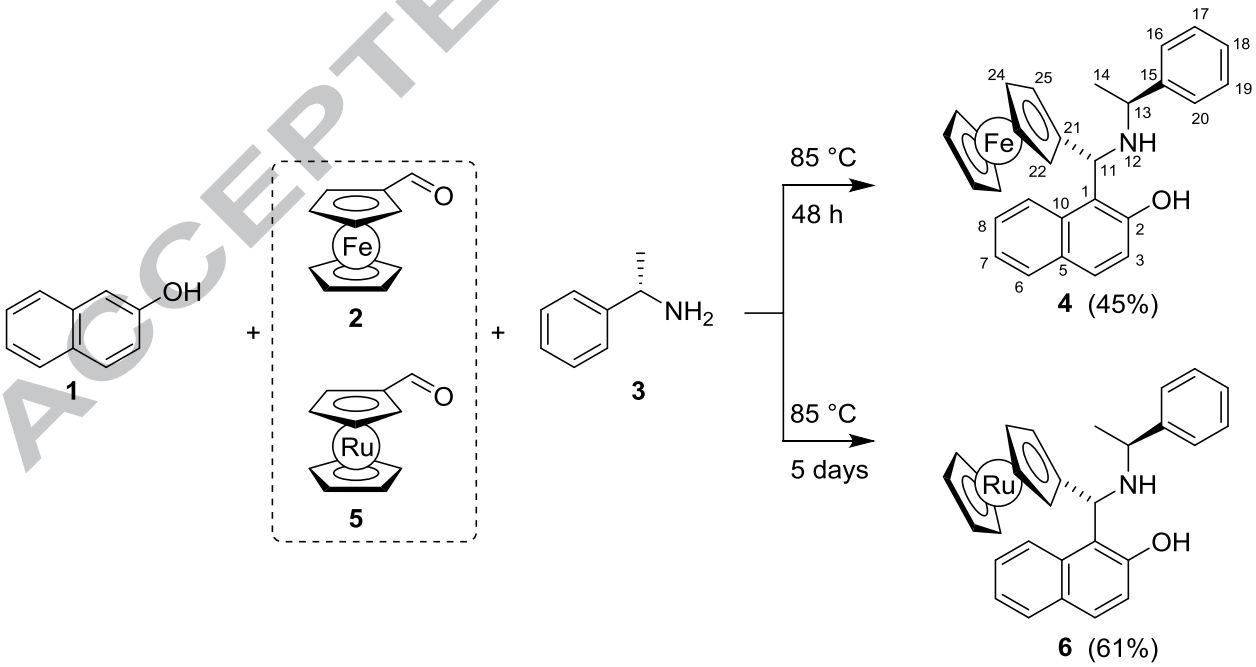
This work describes the use of ferrocene- and ruthenocenecarboxaldehydes in the condensation reaction with 2-naphthol and (*S*)-phenylethylamine, which leads to chiral aminomethylnaphthols incorporating the metallocene core. Chiral compounds with a metallocene core might have various applications in synthesis and catalysis [10].

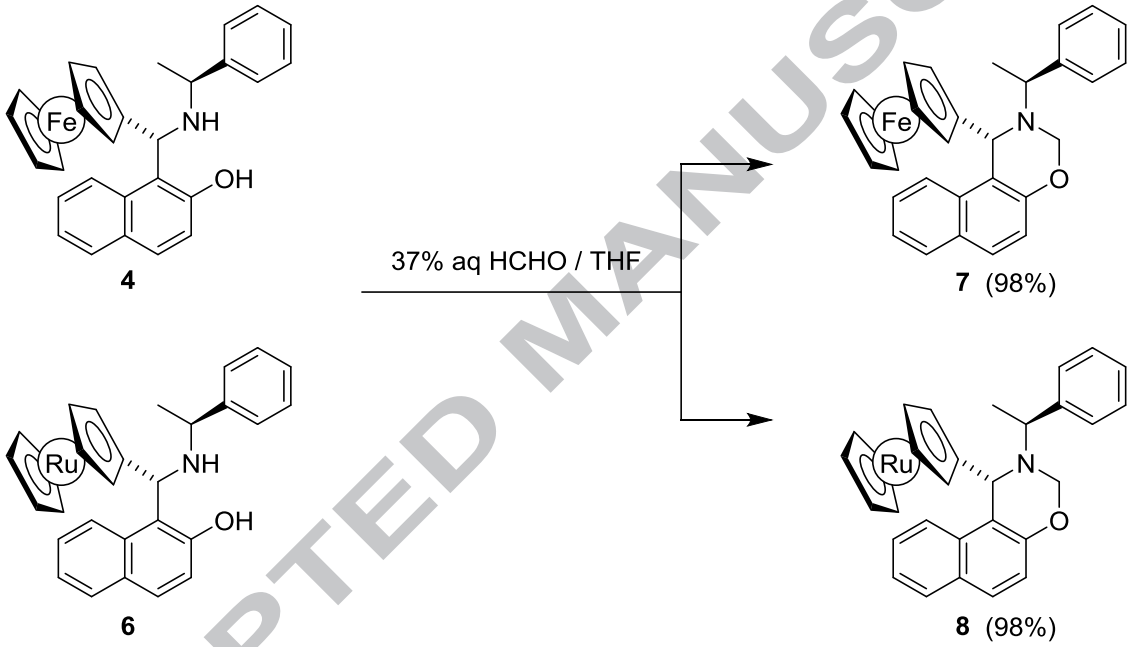
2. Results and discussion

Ferrocene- and ruthenocenecarboxaldehyde were synthesized according to the literature procedure [11]. The initial condensation experiments of 2-hydroxynaphthalene (**1**), ferrocenecarboxaldehyde (**2**) and (*S*)-phenylethylamine (**3**) were performed with refluxing EtOH as the solvent. The formed ferrocenyl-aminomethylnaphthol **4** was isolated after chromatographic purification in low yield (ca. 15%). To realize better yields, the three component condensation was executed without solvent, according to published data [3b,c,e,g,k]. The isolation of the formed product by chromatography brought insufficient improvement of the yields (ca. 16%), probably because of decomposition of the product on the silica gel. Therefore, we performed experiments for crystallization of **4** directly from the crude reaction mixture. The optimized preparation/isolation conditions were to heat a mixture of 2-hydroxynaphthalene (**1**), ferrocenecarboxaldehyde (**2**) and (*S*)-phenylethylamine (**3**) in a 1:1.2:1.5 ratio at 85 °C without solvent for 48 h (Scheme 1) and then to induce crystallization of **4** by adding a 3:1 mixture of methanol/acetone. After recrystallization from the same solvent mixture, the enantiopure ferrocenyl compound **4** was isolated in the pure form as a single diastereoisomer (orange crystals, 45% yield). No other diastereoisomer could be detected in the crude reaction mixture nor in the filtrate after crystallization.



Scheme 1. Condensation of 2-hydroxynaphthalene (**1**), (*S*)-phenylethylamine (**3**) and ferrocenecarboxaldehyde (**2**) or ruthenocenecarboxaldehyde (**5**), leading to the products **4** or **6**, respectively (the numbering of the C-atoms presented on the example of **4** is arbitrary and is used for signal assignment in the NMR spectra).

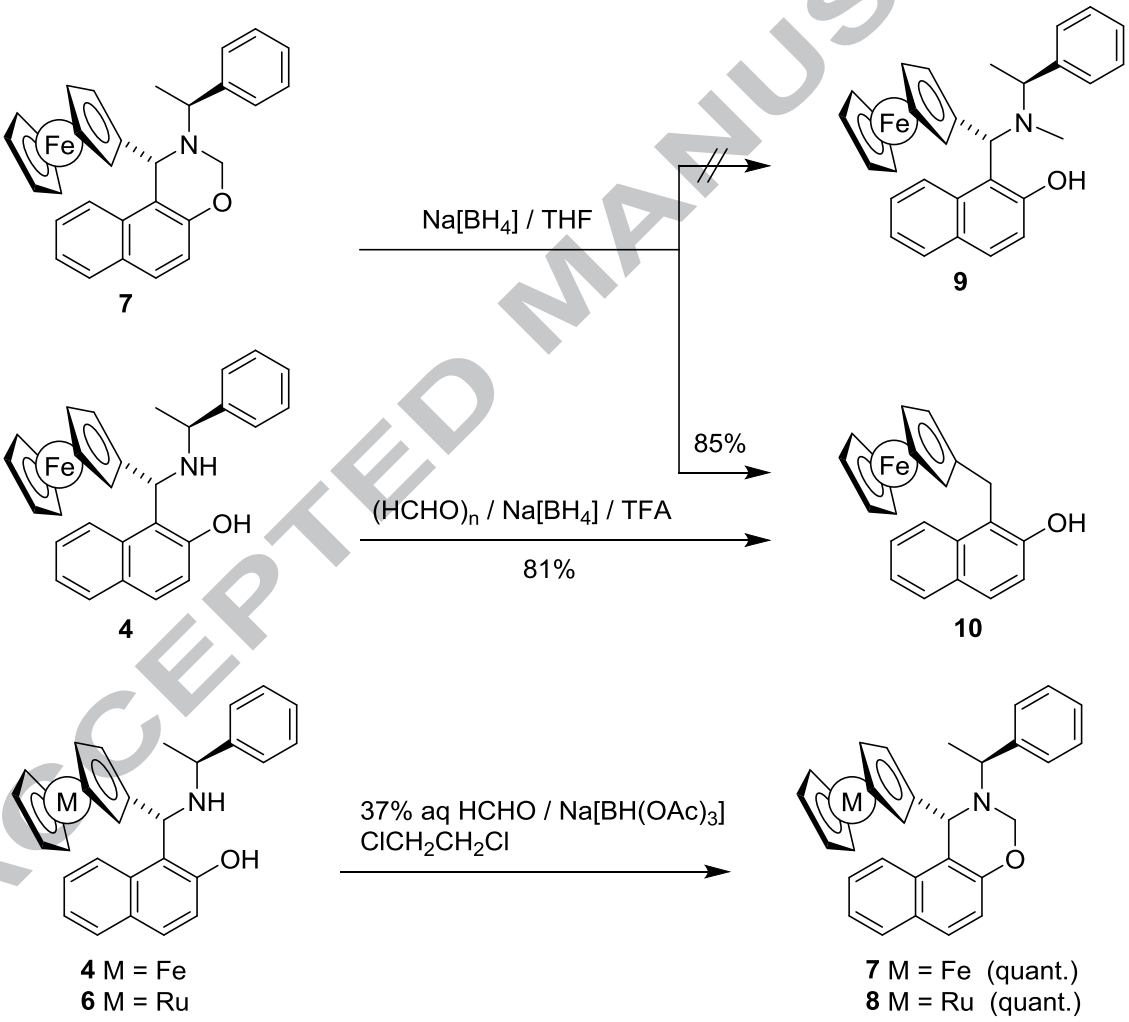
The optimized procedure was applied for the condensation of 2-hydroxynaphthalene (**1**), (*S*)-phenylethylamine (**3**) and ruthenocenecarboxaldehyde (**5**). The reaction was performed at 85 °C without solvent, but in this case the reaction time was prolonged to 5 days (Scheme 1). The product formed was crystallized from the crude mixture using a 3:1 mixture of methanol/acetone. After recrystallization from the same solvent mixture, the ruthenocenyl compound **6** was isolated in the pure form in 61% yield as green crystals, also as an enantiopure single diastereoisomer. No evidence could be found to suggest the presence of a second diastereoisomer. The extraordinarily high diastereoselectivity in the formation of **4** and **6** could be a result of the low stability of the second possible diastereoisomer and/or preferential crystallization of the isolated isomers **4** and **6**, as discussed in published articles [3e,12].



Scheme 2. Synthesis of the 1,3-naphthoxazines **7** and **8**

The metallocene substituted aminomethyl naphthols **4** and **6** were transformed easily into the corresponding dihydronaphthoxazines **7** and **8** through simple mixing with 37% formalin in THF at room temperature (reaction times, 1 h for **4** and 20 h for **6**; Scheme 2). The main reason for obtaining **7** and **8** was the intention to synthesize *N*-methyl substituted derivatives with a suitable reduction reagent. Surprisingly, the attempts to transform **7** into the corresponding *N*-methyl derivative **9** by using Na[BH_4] in THF failed (Scheme 3). Similarly, using the well-established procedure [3d,e,13] to react the ferrocenyl compound **4** with formaldehyde, $NaBH_4$ and TFA in THF did not produce the desired *N*-methyl derivative **9**. Instead, in both cases, the ferrocenylmethyl substituted 2-naphthol **10** was isolated in high yield. These findings were unexpected and curious, since the formation of *N*-methyl aminobenzylnaphthols from their precursor dihydronaphthoxazines by applying similar conditions has been reported [3d,e,n,13]. According to the reported data, the attack of the complex hydride anion should proceed at the bridging CH_2-group between the N and O atoms. This might also be the first step in our case. However, the crucial step is obviously the C11–

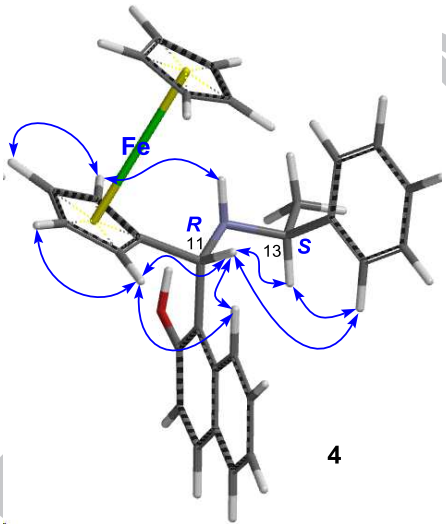
N bond cleavage, which should be considered as a reductive deamination. Reductive deamination has been described to proceed in the presence of $Li[AlH_4]$, using the example of a benzotriazol analogue of phenyl-substituted (instead of metallocenyl-substituted) aminobenzylnaphthol [14]. Reductive deamination has been also realized with aminobenzylnaphthols using a Pd-catalyst [15]. In order to obtain insight into our reaction results, the reaction of **7** with $Na[BD_4]$, instead of $Na[BH_4]$, was performed in the hope of being able to recognize deuterium transfer within the formed product. Unfortunately, no reaction occurred in this case either, even after prolonged reaction times. After these unexpected results, we presumed that it would be pointless to attempt the corresponding experiments with the ruthenocenyl compound **8**. All further attempts to perform reductive amination of compounds **4** and **6** by applying the established procedure using formaline and $Na[BH(OAc)_3]$ in dichloroethane led only to the formation of the corresponding dihydronaphthoxazines **7** and **8**.



Scheme 3. Experiments designed to obtain *N*-methyl derivatives via reductive amination of **4** and **6**.

The configuration determination of the metallocene derivatives **4** and **6** was of particular interest and has been performed using NMR experiments. The ^{1}H and ^{13}C signals of the synthesized compounds were assigned by means of 1D and 2D spectra (DEPT, HSQC and HMBC). The NOESY data provide extensive information about the proton neighborhood around the newly formed stereogenic center (C11), which permitted elucidation of the relative arrangement of the

fragments within the molecule (Fig. 1). The approach provides information about the relative configurations, but taking into account the known absolute configuration of the fragment originating from (*S*)-phenylethylamine, the absolute configuration at C11 could be elucidated. In the NOESY spectra of compounds **4** and **6**, similar proton proximities for the relative positions of the metallocenyl, naphthyl and (*S*)-phenylethylamine parts of the structures could be observed. The most important proton interactions are indicated by means of arrows in Fig. 1. The proton at the newly formed stereogenic center, C11, is in close proximity to the following nuclei: the *peri*-proton from the naphthyl fragment, one of the formal *ortho*-protons from the metallocenyl unit, as well as to the C13 methine proton and an *ortho*-proton of the phenyl moiety. The other *ortho*-proton from the substituted Cp-fragments is located near the NH proton. It should be noted that the OH protons are involved in strong intramolecular O–H···N hydrogen bonding, corroborated by the sharp singlets at δ 13.12 ppm for OH-**4** and at δ 13.40 ppm for OH-**6**. These findings clearly indicate that the arrangement of the metallocenyl, naphthyl and (*S*)-phenylethylamine fragments around the newly formed stereogenic center within compounds **4** and **6** are as presented in Fig.1, which allows one to conclude that C11 has the *R* absolute configuration. The orientations of the Cp-M-fragments shown in the figures are only arbitrary since the NOE interactions with the protons of the unsubstituted Cp-ring were elusive.



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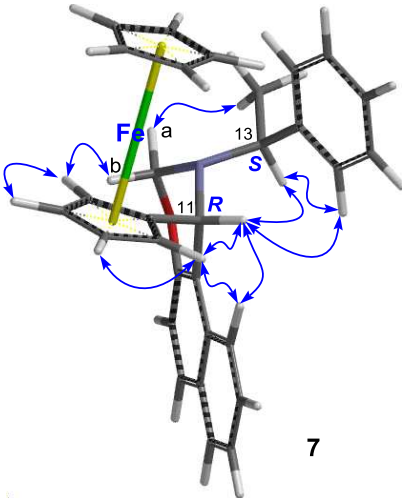

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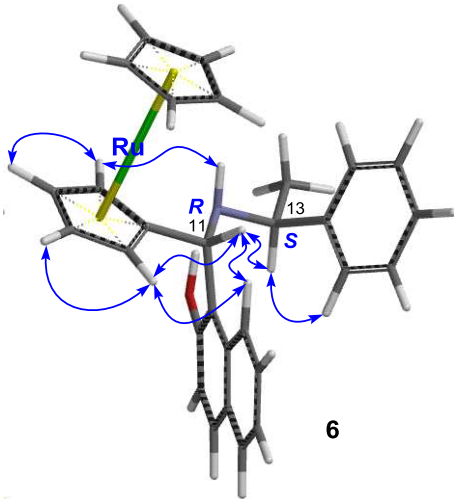

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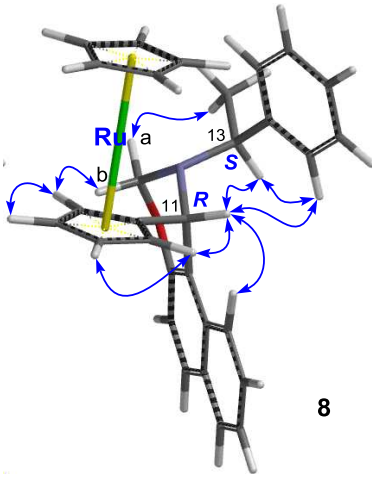

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Fig. 1. Main proton proximities of compounds **4**, **6**, **7** and **8**, observed in the NOESY spectra (images with arbitrary molecular conformations created using Spartan for Windows [16]).

In order to analyze and prove the consistency of the interpretation of the NMR data, the most stable conformations of the four possible diastereoisomers of the ferrocenyl compound **4** were inspected in detail. They are shown in Fig. 2, with the most relevant expected proximities demonstrated with dashed arrows. The NOE proximities are only compatible with the *R*,*S*-**4** isomer. In the case of *S*,*S*-**4**, the C11 proton is in close proximity to the methyl group, but this interaction is not observed in the NOESY spectrum. Another possibility for *R*,*S*-**4** and *S*,*S*-**4** should also be taken into account. As a result of a formal rotation along the C11-naphthyl bond, both isomers could exist as their axially chiral counterparts, ax-*R*,*S*-**4** and ax-*S*,*S*-**4**. The additional interactions between the *peri*-protons from the naphthyl fragments and *ortho*-protons from the metallocenyl units, corresponding to these structures, are also not observed. Consequently, comparison of the experimental NOESY data for compound **4** with the data we might expect for the calculated structures, by considering the observed hydrogen bonding (see also the discussion of the crystal structures), unambiguously confirms that **4** exists in the 11*R*,13*S*-configuration.

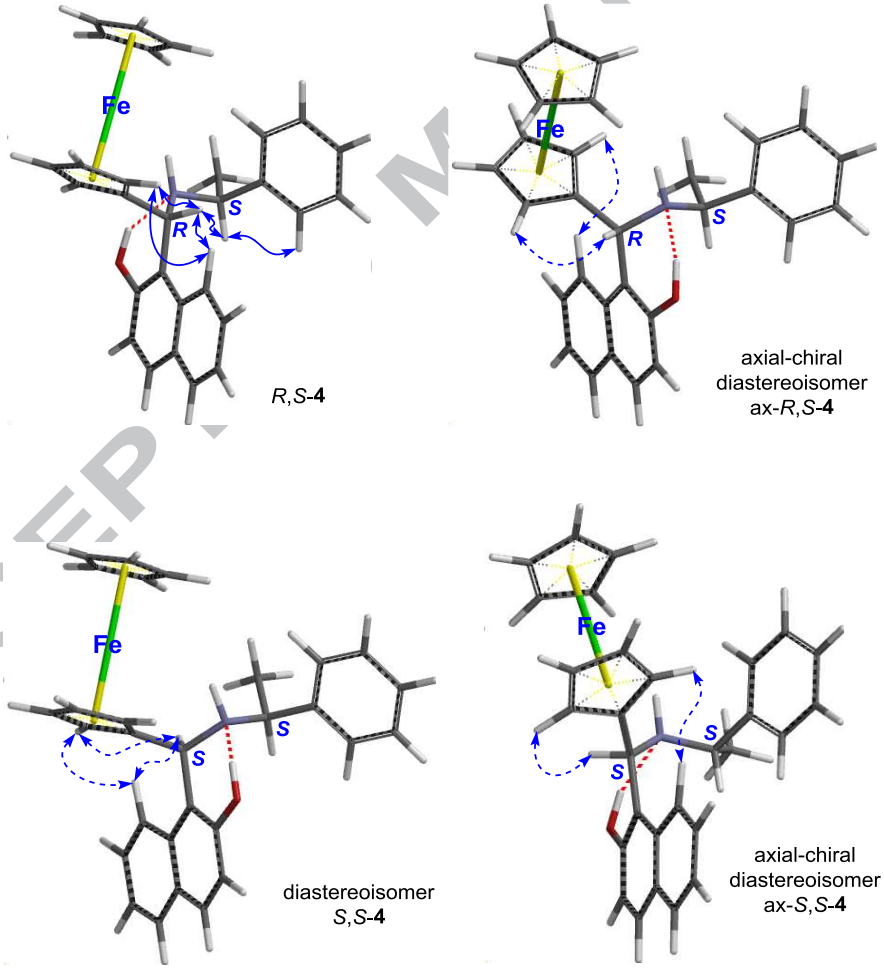


Fig. 2. Expected proton proximities for the four diastereoisomers of compound **4.** Images created using Spartan for Windows [16].

The analysis of the configurations (and conformations) and the above-discussed results for the ferrocenyl and ruthenocenyl compounds **4** and **6** are confirmed by the NOESY data obtained for the corresponding dihydronaphthoxazines **7** and **8** (Fig. 1). The formation of the CH_2-bridge between

the O and N atoms results in a rigid structure, providing the possibility of a reliable configuration elucidation. Complementary information for the proximity of the H_a and H_b protons of the CH_2-bridge relative to the methyl group and to the metallocenyl moiety additionally supports the *R*-configuration of the C11 stereogenic center. It should be noted that the effects are clearly visible in the case of the ruthenocene derivative **8**, because of the well resolved AX proton spin system (H_a 5.14 ppm, H_b δ 5.49 ppm). For the ferrocenyl derivative **7**, these two protons are observed as a complex AB spin system, which precludes unambiguous identification of the proximities of the individual germinal protons. However, the CH_2-bridge of **7** is undoubtedly in close proximity to the methyl- and *ortho*-Cp-protons.

The absolute configurations of compounds **4** and **6** were also independently and unequivocally confirmed by single-crystal X-ray structure analyses (see Section 4.8). Views of the molecules are shown in Fig. 3 and the data collection and refinement parameters are given in Table 1. There are two symmetry-independent molecules of the same enantiomer and with similar conformations in the asymmetric unit of **6**. The root mean square fit of the non-hydrogen atoms of the two molecules is 0.26 Å. Additionally, the crystal of **6** is a merohedral twin resulting from a two-fold rotation about [110]. The major twin component has a twin fraction of 0.6470(7).

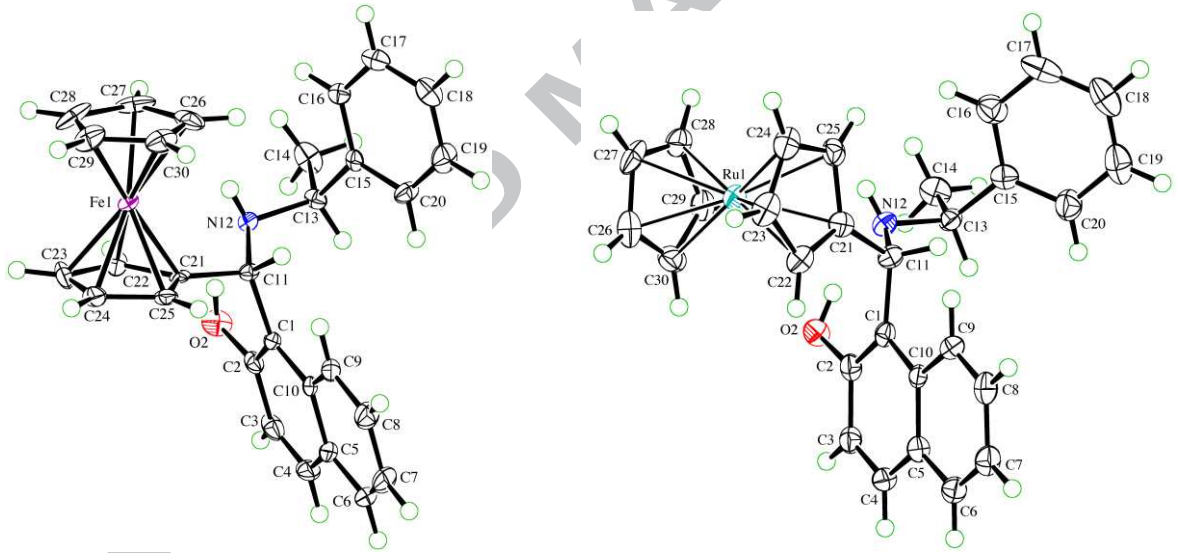


Fig. 3. Displacement ellipsoid plots of the molecular structures of **4** and **6** obtained by X-ray crystallography; only one of the two symmetry-independent, but conformationally quite similar molecules of **6** is shown.

Table 1

Crystal data and structure refinement parameters for **4** and **6**.

Compound	**4**	**6**
Crystallised from	methanol / acetone	methanol / acetone
Empirical formula	$C_{29}H_{27}FeNO$	$C_{29}H_{27}NORu$
M_r (g mol^{-1})	461.38	506.54
Crystal colour, habit	yellow, prism	green, prism

Crystal dimensions (mm)	0.10 × 0.15 × 0.20	0.08 × 0.15 × 0.17
T (K)	160(1)	160(1)
Crystal system	orthorhombic	tetragonal
Space group	$P2_12_12_1$	$P4_3$
Unit cell dimensions		
a (Å)	11.7338(1)	10.1308(2)
b (Å)	12.5834(2)	10.1308(2)
c (Å)	15.4519(2)	44.2398(9)
V (Å^3)	2281.49(5)	4540.5(2)
Z	4	8
F(000)	968	2080
D_{calc} (g cm^{-3})	1.343	1.482
μ(Mo $K\alpha$) (mm^{-1})	0.682	0.712
θ range (°)	2.0–27.5	2.0–27.5
Reflections measured	30907	39528
Symmetry-independent reflections	5178	10115
R_{int}	0.081	0.060
Reflections with $I > 2\sigma(I)$	4543	9128
Reflections used in refinement	5178	10115
Parameters refined; restraints	298; 0	593; 1
$R(F)$ ($I > 2\sigma(I)$ reflections)	0.0505	0.0356
$wR(F^2)$ (all data)	0.1282	0.0619
Goodness of fit on F^2	1.060	1.033
Final Δ_{max}/σ	0.001	0.003
$\Delta\rho_{max}$; $\Delta\rho_{min}$ (e Å^{-3})	0.64; -0.46	0.44; -0.44
Absolute structure parameter	0.005(12)	-0.021(17)
CCDC deposition number	1880618	1880619

The bond lengths and angles in the structures of the complex molecules are within the normal ranges and are unremarkable. The conformations of the organic halves of the molecules of **4** and **6** are very similar. The root mean square fit of the non-hydrogen atoms of this half of the molecule of **4** and those of the molecule of **6** containing the atom C11 is 0.20 Å. However, there is a significantly different relative orientation of the metallocene half of the molecule in the two compounds, primarily because of different torsion angles about the C–C bond linking the organic and metallocene halves of the molecules; C1–C11–C21–C22 in **4** is -94.3(5)°, while the corresponding torsion angles in the two independent molecules of **6** are 11.0(10) and 4.1(10)°. The planes of the cyclopentadienyl rings in both compounds are essentially parallel (the largest dihedral angle is 2.9(3)° in **4**) and the rings are oriented close to an eclipsed conformation; the rotation angles from being perfectly eclipsed rings are 11.7(3)° for **4** and -18.6(6) and 16.1(6)° for the two independent molecules of **6**. In **4**, the Fe atom is 1.641(2) Å from the centroid of the unsubstituted cyclopentadienyl ring and 1.640(2) Å from the centroid of the other cyclopentadienyl ring. The

centroids of the two rings subtend an angle of 177.53(12)° at the Fe atom. In **6**, the corresponding centroid–Ru distances are 1.816(3) and 1.803(3) Å in one of the independent molecules and 1.815(2) and 1.813(3) Å in the other molecule. The subtended angles are 178.55(16) and 179.22(15)°, respectively.

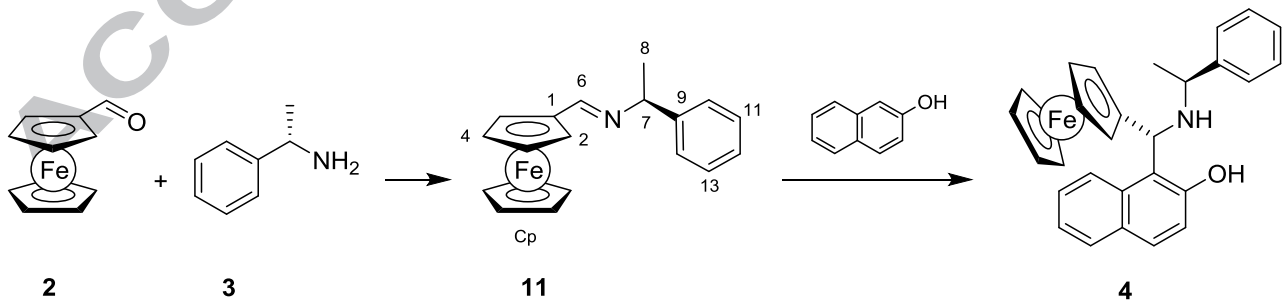
In the structure of each compound, the hydroxy group forms a strong intramolecular hydrogen bond with the amine N atom (Table 2), while the amine group does not act as a donor for any hydrogen bonds because it is too sterically shielded by the surrounding parts of the molecule. There are no significant intermolecular π-π interactions.

Table 2

Intramolecular hydrogen bonding geometry for **4** and **6**.

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)
*Compound **4***				
O2–H2···N12	0.81(6)	1.85(6)	2.606(5)	155(6)
*Compound **6***				
O2–H2···N12	0.84	1.88	2.611(8)	145
O32–H32···N42	0.84(7)	1.88(7)	2.606(8)	143(6)

In order to develop a plausible explanation for the formation mechanism and the diastereoselectivity of the condensation reaction, the ferrocene substituted imine **11** was prepared from **2** and **3**. Its E-configuration was confirmed by NMR spectroscopy. The subsequent reaction of imine **11** with 2-naphthol (**1**) resulted in the formation of **4**, which was isolated again solely as the *R*,*S*-diastereoisomer (17% yield after purification). We have also previously performed the reaction between an imine (obtained from (*S*)-phenylethylamine and 3-methylbenzaldehyde) and 2,6-dihydroxynaphthalene, which led to the formation and isolation of the corresponding arylaminomethylnaphthol [7].



Scheme 4. Formation of imine **11** and its reaction with 2-naphthol to provide **4**.

It is of particular interest to develop a better understanding of the Betti-condensation mechanism. The established opinion is that the Betti-condensation is a special case of a three component Mannich reaction [2d,3e,17]. The discussion of the mechanism is based upon the reaction of a *trans*-imine with 2-naphthol, in which hydrogen bonding is a prerequisite for the C–C bond

formation [3e,12]. The reaction of an imine and 2-naphthol has also been considered as an aza-Friedel-Crafts reaction in the case of C–C bond formation between 3,4-dihydroisoquinoline and 1- or 2-hydroxynaphthalene, which occurs self-catalytically through hydrogen bonding [18].

Our opinion is that the diastereoselectivity is intrinsically connected with the mechanism of the reaction. Taking into account the mechanism and the calculations presented by Palmieri *et al.* [3e], the 2-naphthol molecule approaches the imine (shown in the most suitable conformation in **11-A**) from the *Re*-side of the C=N double-bond, which is assisted by hydrogen bond formation (Fig. 4). The transition complex formed has the lowest energy, according to published calculations [3e], although it cannot be excluded that possible π-π-stacking between the naphthyl and ferrocenyl aromatic cores might play an advantageous role. As a result, there is an enhanced reactivity of both the electrophilic iminium carbon atom and the nucleophilic naphthol moiety. With de-aromatization and re-aromatization of the naphthyl moiety, C–C bond formation leading to *R*,*S*-**4** is realized.

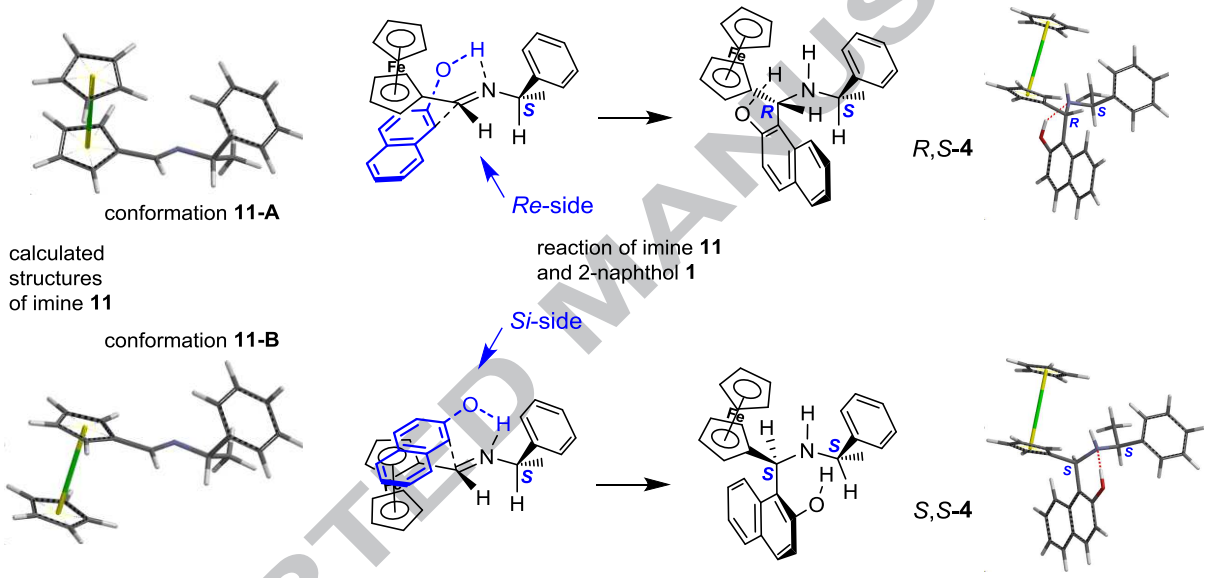


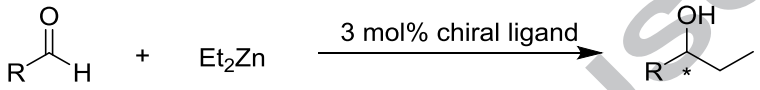
Fig. 4. Proposed mechanism and diastereoselectivity of ferrocenyl-aminomethylnaphthol **4** formation.

A similar situation has to be considered for the 2-naphthol molecule approaching from the *Si*-side of the C=N-double bond. In this case, the imine has to adopt a suitable conformation, as shown in example **11-B** (Fig. 4) for the *Si*-face to be accessible, but the *Si*-side is sterically more hindered compared with the *Re*-side, because the approaching naphthol is then on the same side of the imine plane as the imine phenyl group. Therefore, the formation of the *S*,*S*-diastereoisomer of **4** is less favored. Given that the *S*,*S*-diastereoisomer could not be detected, even in the crude reaction mixture, one could argue that *R*,*S*-**4** is the only diastereoisomer formed. It is also conceivable that the possible *S*,*S*-diastereoisomer has low stability and decomposes under the reaction conditions, so that it cannot be detected.

The synthesized chiral compounds **4** and **6** were tested as pre-catalysts (3 mol%) for the enantioselective addition of Et_2Zn to aldehydes (Table 3) by following a standard procedure [7,19]. In all cases, the yields of the isolated secondary alcohols were very good. The reaction times were usually between 1 and 5 days. In the case of 2,4-dimethylbenzaldehyde, much more time was

required to realize acceptable yields (entries 5 and 14). It should be noted that 2-methoxybenzaldehyde reacts markedly faster, which implies that the methoxy group might be involved in the reaction because of its coordinating ability (entries 2, 10 and 12). The enantioselectivities observed were moderate to high (up to 88% ee) in most cases. The lowest enantioselectivity was obtained with 2,4-dimethylbenzaldehyde, most probably because of the influence of steric and inductive effects (entries 5 and 14). These results suggest that the ferrocene and ruthenocene compounds, **4** and **6** respectively, may be considered to be equally efficient catalysts for the enantioselective addition of Et_2Zn to aldehydes.

Table 3
Enantioselective addition of Et_2Zn to aldehydes catalyzed by ligands **4** and **6**.



Entry	Aldehyde	Ligand	Reaction time (h)	Yield[a] (%)	ee (%), configuration
1	Benzaldehyde	**4**	22	94	63 (*R*)[b]
2	2-Methoxybenzaldehyde	**4**	5	93	84 (*R*)[b]
3	2-Methoxybenzaldehyde	**4**	20 (0 °C)	97	88 (*R*)[b]
4	4-Chlorobenzaldehyde	**4**	30	81	58 (*R*)[b]
5	2,4-Dimethylbenzaldehyde	**4**	78	84	10 (unknown)[b]
6	Ferrocenecarboxaldehyde	**4**	30	78	80 (*R*)[c]
7	2-Naphthaldehyde	**4**	20	89	61 (*R*)[b]
8	Pyrenecarbaldehyde	**4**	48	94	67 (unknown)[c]
9	Benzaldehyde	**6**	22	94	73 (*R*)[b]
10	2-Methoxybenzaldehyde	**6**	5	91	84 (*R*)[c]
11	2-Methoxybenzaldehyde	**6**	20 (0 °C)	91	88 (*R*)[c]
12	2-Methoxybenzaldehyde	**6**	5 (toluene)	82	84 (*R*)[c]
13	4-Chlorobenzaldehyde	**6**	25	81	60 (*R*)[b]
14	2,4-Dimethylbenzaldehyde	**6**	96	80	6 (unknown)[b]
15	2-Naphthaldehyde	**6**	20	92	73 (*R*)[b]

[a] Isolated pure products after column chromatography.

[b] Enantiomeric excess determined by GC analysis.

[c] Enantiomeric excess determined by HPLC analysis. The absolute configuration was determined by comparison of the specific optical rotation with the literature value [20].

3. Conclusions

The three-component "Betti condensation" has efficiently been realized using ferrocene- and ruthenocenecarboxaldehydes as the aldehyde component together with (*S*)-phenylethylamine and 2-hydroxynaphthalene. The metallocenyl-aminomethylnaphthols of iron and ruthenium can easily be transformed into the corresponding dihydrooxazines. The absolute configuration of the newly formed stereogenic center within the synthesized compounds was determined by applying an effective approach based on NMR NOESY experiments. This approach was validated by corresponding X-ray crystal-structure determinations. The ferrocenyl- and ruthenocenyl-aminomethylnaphthols were tested as pre-catalysts for the enantioselective addition of Et_2Zn to aldehydes, providing secondary alcohols with up to 88% enantioselectivity.

4. Experimental

4.1. Materials and instrumentation

Commercial reagents were used for the synthesis of the aminonaphthols, the corresponding dihydrooxazines and for the enantioselective additions. Ferrocenecarboxaldehyde, ruthenocenecarboxaldehyde and ruthenocene were prepared according to the literature [11]. The reactions with Et_2Zn were carried out in flame-dried Schlenk flasks under an argon atmosphere. Hexane was distilled over $Na[Et_4Al]$. The toluene for the enantioselective organozinc additions was dried by refluxing over $Li[AlH_4]$ and distilled under an argon atmosphere. Thin layer chromatography (TLC) was performed on aluminum sheets pre-coated with Merck Kieselgel 60 F_{254} 0.25 mm (Merck). Flash column chromatography was carried out using Silica Gel 60 230–400 mesh, (Merck). The melting points of the compounds were determined by using BOETIUS, type PHMK 05 (uncorrected). Optical rotation $[\alpha]_D^{20}$ measurements were obtained using a Perkin-Elmer 241 polarimeter. The NMR spectra were recorded on a Bruker DRX 250 (250.13 MHz for ^{1}H NMR, 62.9 MHz for ^{13}C NMR; 298K) and Bruker Avance II+ 600 (600.13 MHz for ^{1}H NMR, 150.92 MHz for ^{13}C NMR; 293K) spectrometers with TMS as the internal standard for chemical shifts (δ, ppm). ^{1}H and ^{13}C NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration and identification. The assignment of the ^{1}H and ^{13}C NMR spectra was made on the basis of DEPT, HSQC, HMBC and NOESY experiments. Cp stands for cyclopentadienyl. All assignments marked with an asterisk are tentative. Mass spectra (MS) were recorded on a Thermo Scientific DFS (Double Focusing Magnetic Sector) mass spectrometer using electron impact (EI) techniques (70 eV), with the results reported as fragmentation in *m/z* with relative intensities (%) in parentheses. High performance liquid chromatography (HPLC) separations were performed with an Agilent 1100 system fitted with a diode array detector and a manual injector with a 20 μL injection loop. Gas chromatography (GC) was performed with a Shimadzu GC-17A. Elemental analyses were performed by the Microanalytical Service Laboratory of the Institute of Organic Chemistry with the Centre of Phytochemistry, Bulgarian Academy of Sciences.

4.2. Synthesis of the chiral aminonaphthols

*4.2.1. 1-((R)-Ferrocenyl((S)-1-phenylethylamino)methyl)naphthalene-2-ol (**4**)*

A mixture of naphthalene-2-ol (**1**) (0.173 g, 1.20 mmol), ferrocenecarboxaldehyde (**2**) (0.308 g, 1.44 mmol) and (*S*)-(-)-1-phenylethylamine (**3**) (0.218 g, 1.80 mmol) was stirred at 85 °C for 2 days. To the crude reaction melt, a mixture of methanol/acetone (3:1) was added, which caused the formation of crystals from the product. After recrystallization from methanol/acetone (3:1), the pure product was isolated as orange crystals, 0.250 g (45%). Mp: 165–167 °C. $[\alpha]_D^{20}$ = +30.8 (*c* 1.00, $CHCl_3$). Anal. Calc. for $C_{29}H_{27}FeNO$ (461.386): C, 75.49; H, 5.90; Fe, 12.10; N, 3.04. Found: C, 75.20; H, 5.61; Fe, 12.45; N, 3.18%. MS (EI) *m/z* (rel. int.): 461 (M^+, 3), 340 (100), 275 (84), 219 (22), 189 (38), 106 (46), 79 (13). ^{1}H NMR (600.13 MHz, $CDCl_3$) δ, ppm: 1.56 (d, *J* = 6.8 Hz, 3H, H-14), 2.75 (d, *J* = 11.6 Hz, 1H, NH), 3.78 (dq, *J* = 11.6; 6.8 Hz, 1H, H-13), 3.95 (s, 5H, Cp), 3.99 (dt, *J* = 1.3; 2.5 Hz, 1H, H-23), 4.02 (dt, *J* = 1.3; 2.5 Hz, 1H, H-24), 4.09 (dt, *J* = 2.5; 1.3 Hz, 1H, H-22), 4.24 (dt, *J* = 2.5; 1.3 Hz, 1H, H-25), 5.17 (s, 1H, H-11), 7.09 (d, *J* = 8.8 Hz, 1H, H-3), 7.19–7.20 (m, 2H, H-16, H-20), 7.25 (ddd, *J* = 7.5; 6.8; 1.0 Hz, 1H, H-7), 7.35–7.41 (m, 4H, H-8, H-17, H-18, H-19), 7.61 (d, *J* = 8.6 Hz, 1H, H-9), 7.65 (d, *J* = 8.8 Hz, 1H, H-4), 7.72 (dd, *J* = 7.5; 1.0 Hz, 1H, H-6), 13.12 (s, 1H, OH). ^{13}C NMR (150.92 MHz, $CDCl_3$) δ, ppm: 22.56 (q, C-14), 53.39 (d, C-11), 55.57 (d, C-13), 65.58 (d, C-25), 66.85 (d, C-22), 67.51 (d, C-24), 67.77 (d, C-23), 68.46 (d, 5C, Cp), 91.35 (s, C-21), 115.43 (s, C-1), 119.85 (d, C-3), 121.25 (d, C-9), 122.22 (d, C-7), 126.09 (d, C-8), 126.83 (2d, C-16, C-20), 127.94 (d, C-18), 128.68 (s, C-5), 128.90 (d, C-6), 128.91 (2d, C-17, C-19), 129.24 (d, C-4), 132.46 (s, C-10), 142.99 (s, C-15), 156.23 (s, C-2).

*4.2.2. 1-((R)-Ruthenocenyl((S)-1-phenylethylamino)methyl)naphthalene-2-ol (**6**)*

A mixture of naphthalene-2-ol (**1**) (0.556 g, 3.86 mmol), (*S*)-(-)-1-phenylethylamine (**3**) (0.842 g, 6.95 mmol) and ruthenocenecarboxaldehyde (**5**) (1.000 g, 3.86 mmol) was stirred at 85 °C for 5 days. To the crude reaction melt, a mixture of methanol/acetone (3:1) was added, which caused the formation of crystals from the product. After recrystallization from methanol/acetone (3:1), the pure product was isolated as green crystals, 1.200 g (61%). Mp: 158-159 °C. $[\alpha]_D^{20}$ = +9.9 (*c* 1.000, $CHCl_3$). Anal. Calc. for $C_{29}H_{27}NORu$ (506.611): C, 68.75; H, 5.37; N, 2.76; Ru, 19.95. Found: C, 68.58; H, 5.32; N, 3.03; Ru, 20.15%. MS (EI) *m/z* (rel. int.): 507 (M^+, 7), 386 (100), 356 (37), 106 (13), 79 (3). ^{1}H NMR (600.13 MHz, $CDCl_3$) δ, ppm: 1.50 (d, *J* = 6.9 Hz, 3H, H-14), 2.59 (d, *J* = 10.4 Hz, 1H, NH), 3.73 (dq, *J* = 10.4; 6.9 Hz, 1H, H-13), 4.34 (dt, *J* = 1.3; 2.3 Hz, 1H, H-23), 4.36 (dt, *J* = 1.1; 2.3 Hz, 1H, H-24), 4.43 (s, 5H, Cp), 4.57 (dt, *J* = 2.3; 1.1 Hz, 1H, H-22), 4.72 (dt, *J* = 1.1; 2.3 Hz, 1H, H-25), 4.92 (s, 1H, H-11), 7.09 (d, *J* = 8.8 Hz, 1H, H-3), 7.13–7.15 (m, 2H, H-16, H-20), 7.24 (ddd, *J* = 8.0; 6.8; 1.0 Hz, 1H, H-7), 7.33–7.37 (m, 4H, H-17, H-19, H-8, H-18), 7.54 (d, *J* = 8.6 Hz, 1H, H-9), 7.65 (d, *J* = 8.8 Hz, 1H, H-4), 7.72 (dd, *J* = 8.0;1.0 Hz, 1H, H-6), 13.40 (s, 1H, OH). ^{13}C NMR (150.92 MHz, $CDCl_3$) δ, ppm: 22.64 (q, C-14), 52.91 (d, C-11), 55.79 (d, C-13), 68.79 (d, C-25), 69.64 (d, C-22), 70.06 (d, C-23), 70.18 (d, C-24), 70.85 (d, 5C, Cp), 96.24 (s, C-21), 115.01 (s, C-1), 119.90 (d, C-3), 121.14 (d, C-9), 122.19 (d, C-7), 126.10 (d, C-8), 126.70 (2d, C-16, C-20), 127.80 (d, C-18), 128.63 (s, C-5), 128.83 (2d, C-17, C-19), 128.88 (d, C-6), 129.24 (d, C-4), 132.51 (s, C-10), 142.96 (s, C-15), 156.32 (s, C-2).

*4.3. Synthesis of the 1,3-naphthoxazines **7** and **8***

*4.3.1. (R)-1-(Ferrocenyl)-2-((S)-1-phenylethyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (**7**)*

To a solution of **4** (0.050 g, 0.108 mmol) in THF (1 mL) was added a 37% aq solution of formaldehyde (calculated to provide 10 equivalents of formaldehyde) and the mixture was stirred at 20 °C for 1 h. After evaporation of the solvent, the crude product was purified by column chromatography (Φ = 14 mm, h = 160 mm, 7 g silica gel, hexane/Et_2O = 6:1) to give 0.050 g (98%) of **7** as yellow crystals. Mp: 173–176 °C. $[\alpha]_D^{20}$ = +208.3 (*c* 1.000, $CHCl_3$). Anal. Calc. for $C_{30}H_{27}FeNO$ (473.397): C, 76.12; H, 5.75; Fe, 11.80; N, 2.96. Found: C, 76.04; H, 5.71; Fe, 11.64; N, 3.02%. MS (EI) *m/z* (rel. int.): 473 (M^+, 8), 340 (100), 275 (86), 219 (18), 189 (28), 105 (54), 77 (9). ^{1}H NMR (250.13 MHz, $CDCl_3$) δ, ppm: 1.52 (d, *J* = 6.6 Hz, 3H, H-14), 3.70 (dt, *J* = 2.4; 1.2 Hz, 1H, H-22), 3.85 (q, *J* = 6.6 Hz, 1H, H-13), 3.90 (s, 5H, Cp), 3.92 (dt, *J* = 1.3; 2.4 Hz, 1H, H-23), 4.03 (dt, *J* = 1.2; 2.4 Hz, 1H, H-24), 4.60 (dt, *J* = 2.3; 1.3 Hz, 1H, H-25), 5.12–5.22 (m, 2H, H-26), 5.28 (s, 1H, H-11), 7.01 (d, *J* = 8.9 Hz, 1H, H-3), 7.29–7.47 (m, 7H, H-7, H-8, H-16, H-17, H-18, H-19, H-20), 7.64 (d, *J* = 8.9 Hz, 1H, H-4), 7.75 (dd, *J* = 8.1; 1.6 Hz, 1H, H-6), 7.89 (d, *J* = 8.4 Hz, 1H, H-9). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ, ppm: 21.63 (q, C-14), 53.13 (d, C-11), 58.07 (d, C-13), 66.57 (d, C-24), 67.30 (d, C-23), 68.18 (d, C-25), 69.12(d, 5C, Cp), 69.29 (d, C-22), 74.42 (t, C-26), 92.58 (s, C-21), 115.56 (s, C-1), 118.67 (d, C-3), 122.98 (d, C-7), 123.52 (d, C-9), 125.76 (d, C-18), 127.35 (3d, C-8, C-16, C-20), 128.26 (d, C-4), 128.47 (3d, C-6, C-17, C-19), 128.98 (s, C-5), 133.25 (s, C-10), 145.77 (s, C-15), 151.18 (s, C-2).

*4.3.2. (R)-1-(Ruthenocenyl)-2-((S)-1-phenylethyl)-2,3-dihydro-1H-naphtho[1,2-e][1,3]oxazine (**8**)*

To a solution of **6** (0.200 g, 0.395 mmol) in THF (2 ml) was added a 37% aq solution of formaldehyde (calculated to provide 10 equivalents of formaldehyde) and the mixture was stirred at 20 °C for 20 h. After evaporation of the solvent, the crude product was purified by column chromatography (Φ = 13 mm, h = 300 mm, 10 g silica gel, hexane/Et_2O = 6:1) to give 0.200 g (98%) of **8** as white crystals. Mp 168–170 °C. $[\alpha]_D^{20}$ = +175.7 (*c* 1.000, $CHCl_3$). Anal. Calc. for $C_{30}H_{27}NORu$ (518.622): C, 69.48; H, 5.25; N, 2.70; Ru, 19.49. Found: C, 69.63; H, 5.49; N, 2.82; Ru, 19.70%. MS (EI) *m/z* (rel. int.): 519 (M^+, 2), 386 (100), 356 (48), 105 (66), 79 (8). ^{1}H NMR (250.13 MHz, $CDCl_3$) δ, ppm: 1.49 (d, *J* = 6.6 Hz, 3H, H-14), 3.80 (q, *J* = 6.6 Hz, 1H, H-13), 4.27 (dtd, *J* = 2.4; 1.1; 0.4 Hz, 1H, H-22), 4.33 (s, 5H, Cp), 4.35 (dt, *J* = 1.2; 2.3 Hz, 1H, H-23), 4.39 (dt, *J* = 1.2; 2.3 Hz, 1H, H-24), 4.83 (dtd, *J* = 2.3; 1.1; 0.3 Hz, 1H, H-25), 5.01 (s, 1H, H-11), 5.14 (dd, *J* = 10.8, 2.0 Hz, 1H, H_a-26), 5.49 (dd, *J* = 10.8, 0.9 Hz, 1H, H_b-26), 7.04 (d, *J* = 8.9 Hz, 1H, H-3), 7.24–7.37 (m, 7H, H-7, H-8, H-17, H-19, H-18, H-16, H-20), 7.63-7.66 (m, 2H, H-4, H-9), 7.70–7.74 (m, 1H, H-6). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ, ppm: 21.74 (q, C-14), 52.40 (d, C-11), 58.21 (d, C-13), 69.22 (d, C-24), 69.65 (d, C-23), 71.11 (d, C-25), 71.35 (d, C5, Cp), 72.56 (d, C-22), 74.40 (t, C-26), 96.81 (s, C-21), 115.41 (s, C-1), 118.56 (d, C-3), 122.94 (d, C-7), 123.82 (d, C-9), 125.72 (d, C-8), 127.16 (d, C-18), 127.26 (2d, C-16, C-20), 128.31 (2d, C-4, C-6), 128.37 (2d, C-17, C-19), 128.91 (s, C-5), 133.14 (s, C-10), 145.63 (s, C-15), 151.32 (s, C-2).

*4.4. Experiments for the preparation of N-methylated **4** and **6***

*4.4.1. Reaction of **7** with Na[BH_4].*

To a solution of **7** (0.065 g, 0.137 mmol) in THF (3 mL), Na[BH_4] (0.011 g, 0.28 mmol) was added and the reaction mixture was stirred at 20 °C for 24 h. An additional quantity of Na[BH_4] (0.011 g, 0.28 mmol) in methanol (2 mL) was added and the reaction mixture was stirred at room temperature for a further 24 h. After that time, a further quantity of Na[BH_4] (0.011 g, 0.28 mmol) was added and the reaction mixture was refluxed for 6 h. The solvent was evaporated, CH_2Cl_2 was added and the organic phase was washed with H_2O and dried over Na_2SO_4. The crude product was purified by column chromatography (Φ = 10 mm, h = 160 mm, 6 g silica gel, hexane/Et_2O = 20:1) to give 0.040 g (85%) of 1-(ferrocenylmethyl)-naphthalene-2-ol (**10**) as orange crystals. Mp: 111–112 °C. MS (EI) *m*/z (rel. int.): 342 (M^+, 100), 258 (47), 202 (54), 121 (21), 56 (8). ^{1}H NMR (250.13 MHz, $CDCl_3$) δ, ppm: 3.98-4.06 (m, 2H, H-11), 4.12–4.17 (m, 4H, H-13, H-14, H-15, H-16, in it 4.15 (s, 5H, Cp)), 5.26 (s, 1H, OH), 7.04 (d, *J* = 8.8 Hz, 1H, H-3), 7.31 (t, *J* = 7.4 Hz, 1H, H-7), 7.47 (t, *J* = 7.4 Hz, 1H, H-8), 7.63 (d, *J* = 8.8 Hz, 1H, H-4), 7.75 (d, *J* = 8.1 Hz, 1H, H-6), 7.98 (d, *J* = 8.5 Hz, 1H, H-9). ^{13}C NMR (62.9 MHz, $CDCl_3$) δ, ppm: 24.82 (t, C-11), 67.26 (2d, C_{Fe}), 68.55 (2d, C_{Fe}), 68.81 (d, 5C, Cp), 87.39 (s, C-12), 117.91 (d, C-3), 119.12 (s, C-1), 123.07 (d, C-9), 123.29 (d, C-7), 126.32 (d, C-8), 128.09 (d, C-4), 128.51 (d, C-6), 129.36 (s, C-5), 133.16 (s, C-10), 150.70 (s, C-2). Assignment of the aromatic signals is tentative.

*4.4.2. Reaction of **4** with $(CH_2O)_n$/Na[BH_4]/TFA*

To a solution of **4** (0.050 g, 0.108 mmol) in THF (2 mL), paraformaldehyde (0.033 g, 1.100 mmol), Na[BH_4] (0.042 g, 1.100 mmol) and a solution of TFA (0.627 g, 5.50 mmol) in THF (2.5 mL) were added. The reaction mixture was stirred at room temperature for 24 h, and then it was quenched with 10% K_2CO_3 and extracted with CH_2Cl_2. The organic phase was washed with water, dried over anhydrous Na_2SO_4 and the solvent evaporated *in vacuo*. The crude product was purified by column chromatography (Φ = 13 mm, h = 220 mm, 8 g silica gel, hexane/Et_2O = 10:1) to give 0.030 g (81%) of **10**. The NMR data were identical with those described in 4.4.1.

*4.4.3. Reaction of **4** or **6** with 37% aq HCHO/Na[$BH(OAc)_3$]*

To a solution of **4** or **6** (1 equivalent) in 1,2-dichloroethane (6 mL), a 37% aq solution of formaldehyde (calculated to provide 2 equivalents of formaldehyde) and Na[$BH(OAc)_3$] (1.6 equivalents) were added. After stirring at room temperature for 0.5 h, the formation of the corresponding naphthoxazines was detected with no remaining starting compounds (TLC data). The reaction mixtures were stirred for 24 h and then AcOH (2 equivalents) was added. After an additional 96 h, the reaction mixtures were quenched with 10% K_2CO_3 and extracted with CH_2Cl_2. The organic phases were washed with water, dried over anhydrous Na_2SO_4 and the solvent evaporated *in vacuo*. The naphthoxazines **7** and **8** were isolated quantitatively as yellow or colorless crystals, respectively. The NMR data of the products **7** and **8** were identical with those described in 4.3.1 and 4.3.2, respectively.

*4.5. (S)-1-Ferrocenyl-N-(1-phenylethyl)methanimin (**11**)*

To a solution of ferrocenecarboxaldehyde (**2**) (0.100 g, 0.467 mmol) in dry CH_2Cl_2 (5 mL), (*S*)-(-)-1-phenylethylamine (**3**) (0.057 g, 0.467 mmol) was added at room temperature under an Ar atmosphere and in the presence of anhydrous Na_2SO_4. The reaction mixture was refluxed for 48 h (monitored by TLC on aluminum sheets pre-coated with silica gel and deactivated with Et_3N, petroleum ether/Et_2O = 2:1). The reaction mixture was filtered through a pad of Celite and washed with CH_2Cl_2. After evaporation of the solvent, 0.142 g (96%) of the product **11** were isolated. ^{1}H NMR (600.13 MHz, $CDCl_3$) δ, ppm: 1.58 (d, J = 6.7 Hz, 3H, H-8), 4.11 (s, 5H, Cp), 4.34–4.36 (m, 2H, H-3, H-4), 4.42 (q, J = 6.7 Hz, 1H, H-7), 4.64 (dt, J = 2.4; 1.3 Hz, 1H, H-2*), 4.71 (dt, J = 2.4; 1.3 Hz, 1H, H-5*), 7.22–7.25 (m, 1H, H-12), 7.32–7.35 (m, 2H, H-11,H-13), 7.37–7.40 (m, 2H, H-10,H-14), 8.21 (s, 1H, H-6). ^{13}C NMR (150.9 MHz, $CDCl_3$,) δ, ppm: 24.19 (q, C-8), 68.28, 68.89 (2d, C_5H_4 and/or 7), 68.95 (5C, Cp), 69.40, 70.35, 70.40 (3d, C_5H_4 and/or 7), 80.62 (s, C-1), 126.53*(2d, C-10, C-14), 126.68 (d, C-12), 128.35*(2d, C-11,C-13), 145.26 (s, C-9), 159.66 (d, C-6). The NMR data are in consistence with the literature data [21].

4.6. General procedure for the enantioselective addition of diethylzinc to aldehydes

To a solution of the corresponding ligand **4** and **6** (3 mol %) in hexane (10 mL) or toluene (10 mL), Et_2Zn (1.7 equivalents of a 1 M solution in hexane) was added dropwise at 0 °C. The mixture was stirred for 30 min at 0 °C and then the corresponding aldehyde (1 equivalent) was added at -20 °C. The reaction was stirred at room temperature and monitored by TLC (PE/Et_2O = 4:1) until the aldehyde was consumed. The mixture was quenched (aq NH_4Cl), extracted with Et_2O (3 × 20 ml) and dried. After evaporation of the solvent, the crude product was purified by column chromatography (PE/Et_2O = 20:1). The enantiomeric excess of the products was determined by GC or HPLC with chiral columns.

4.7. Conditions for the determination of enantiomeric excess (GC or HPLC)

1-Phenylpropan-1-ol determined by GC analysis (Hydrodex β-TBDAc column, 122 °C isothermal, 1 ml/min He, split 21:1, T_{det} = 220 °C, T_{inj} = 220 °C) retention time t_R = 9.4 min, t_S = 9.8 min. 1-(2-Methoxyphenyl)propan-1-ol determined by GC analysis (FS-Cyclodex beta-I/P, 150 °C isothermal, 1 ml/min He, split 22:1, T_{det} = 220 °C, T_{inj} = 220 °C) retention time t_S = 9.6 min, t_R = 10.0 min. 1-(2,4-Dimethylphenyl)propan-1-ol determined by GC analysis (FS-Cyclodex beta-I/P, 145 °C isothermal, 1 ml/min He, split 21:1, T_{det} = 230 °C, T_{inj} = 220 °C) retention time t_{major} = 10.3 min, t_{minor} = 10.8 min. 1-(4-Chlorophenyl)propan-1-ol determined by GC analysis (FS-Cyclodex beta-I/P column, 145 °C isothermal, 1 ml/min He, split 21:1, T_{det} = 230 °C, T_{inj} = 220 °C) retention time t_R = 13.6 min, t_S = 14.2 min. 1-Ferrocenylpropan-1-ol determined by HPLC analysis (Chiralpak IC column, 5% *i*-PrOH in hexane, 1 ml/min, 213 nm DAD detector) retention time t_S = 7.6 min, t_R = 8.1 min. 1-(Naphthalen-2-yl)propan-1-ol determined by GC analysis (Hydrodex β-TBDAc column, 160 °C isothermal, 1 ml/min He, split 21:1, T_{det} = 240 °C, T_{inj} = 240 °C) retention time t_R = 26.7 min, t_S = 27.5 min. 1-(Pyren-1-yl)propan-1-ol determined by HPLC analysis (Nucleosil Chiral-2 column, 5% *i*-PrOH in hexane, 1 ml/min, 242 nm DAD detector) retention time t_{minor} = 12.1 min, t_{major} = 13.0 min.

4.8. Crystal structure determinations

All crystallographic measurements for complexes **4** and **6** were performed on a Nonius Kappa CCD area-detector diffractometer [22] using graphite-monochromated Mo$K\alpha$ radiation (λ = 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. Data reduction was performed with HKL Denzo and Scalepack [23]. The intensities were corrected for Lorentz and polarization effects and absorption corrections based on the multi-scan method [24] were applied. Equivalent reflections, other than Friedel pairs, were merged. The structure of **4** was solved by direct methods using SIR92 [25], while that of **6** was solved by heavy-atom Patterson methods and Fourier expansion using the program DIRDIF94 [26]. There are two symmetry-independent molecules in the asymmetric unit of **6**. The atomic coordinates of the two molecules were tested carefully for a relationship from a higher symmetry space group using the program PLATON [27], but none could be found. Initial refinement of the model yielded poor results and analysis with PLATON revealed that the crystal is a merohedral twin resulting from a two-fold rotation about [110]. The twin matrix is [0 1 0 / 1 0 0 / 0 0 -1] and the major twin component has a twin fraction of 0.6470(7). The non-H atoms of each structure were refined anisotropically. The amine and hydroxy H atoms of **4** and the amine and one hydroxy H atoms of **6** were placed in the positions indicated by a difference electron density map and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H atoms were placed in geometrically calculated positions and refined by using a riding model where each H atom was assigned a fixed isotropic displacement parameter with a value equal to $1.2U_{eq}$ of its parent C atom. The refinement of each structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. Refinement of the absolute structure parameter [28,29] confidently confirmed that in each case the refined model corresponds with the true enantiomorph. All calculations were performed using the SHELXL2018 [30] program. The data collection and refinement parameters are given in Table 1 and views of the molecules are shown in Fig. 3.

Acknowledgements

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Appendix A. Supplementary data

CCDC 1880618 and 1880619 contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

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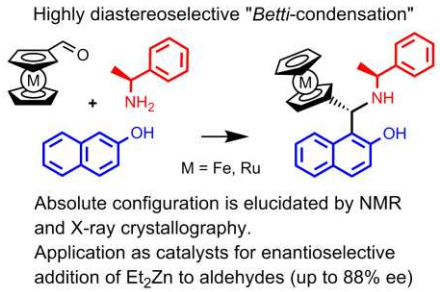

Graphical Abstract

Krasimira Dikova, Kalina Kostova, Svetlana Simova, Anthony Linden, Angel Chimov and Vladimir Dimitrov

Synthesis and crystal structures of chiral ferrocene and ruthenocene substituted aminomethylnaphthols obtained through Betti-condensation

Ferrocene- and ruthenocenecarboxaldehydes have been employed in Betti-type condensation reactions with 2-naphthol and (*S*)-phenylethylamine to give metallocenyl-substituted aminomethylnaphthols in a diastereomerically pure form. The absolute configurations of the new chiral compounds have been determined by means of NMR experiments and confirmed by X-ray crystallography. The chiral metallocenyl-aminomethylnaphthols have been tested as pre-catalysts for the addition of diethyl zinc to aldehydes with enantioselectivities of up to 88% ee.